A historical perspective towards a non-invasive treatment for patients with atherosclerosis

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The history of atherosclerosis and cardiovascular disease dates back to ancient times. From the teachings of Galen to the response-to-injury hypothesis of Russel Ross, we have now arrived at the concept of the vulnerable plaque. Next to the development of new treatment options for patients with atherosclerosis, also novel diagnostic imaging techniques have been developed to visualise the arterial wall and to characterise plaque composition. In this article the historical context of atherosclerosis and the attempts towards a non-invasive therapy for patients with atherosclerotic diseases are described. (*Neth Heart J* 2009;17:140-5.)

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In the Roman Empire a famous doctor named Galen (131-201 AD) was the first to describe the heart and the movement of blood in the arteries.[1] Galen was convinced that the heart acted by sucking the blood from the veins and that it flowed through the septum of the heart through tiny pores. For over 1000 years most doctors accepted the teachings of Galen, but it was the British physician William Harvey (1578-1657) who discovered the circulation of blood in 1628.[2] He wondered how Galen, being so close to the answer, did not himself arrive at the concept of circulation. He could not see capillaries at that time, which were first described in 1674 by Malpighi with the help of advances in microscopy.

Among the first to describe atherosclerosis was Leonardo da Vinci (1452-1519),[3] who stated that 'vessels in the elderly restrict the transit of blood through thickening of the tunics'. In 1768, the symptoms of angina pectoris were described by the British doctor William Heberden:[4] 'They who are afflicted with it are seized while they are walking with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue; but the moment they stand still, all uneasiness vanishes'. Some years later, in 1799, Caleb Hillier Parry, a British physician (1755-1822), made a major contribution to medicine by the recognition of the cause of angina. He conducted experiments on sheep to investigate the circulation and the effects of impairment of the vascular supply. During an autopsy he found a gritty substance in coronary arteries. His first impression was that some plaster had fallen from the ceiling, but upon closer investigation he discovered that the plaster-like substance was within the arteries themselves. He was the first to suggest the correct mechanism of ischaemic heart disease, although his explanation was ignored for more than 100 years. Plaque rupture was reported for the first time during the autopsy of Bertel Thorvaldsen, a celebrated neoclassical Danish artist and sculptor who died of sudden cardiac death in the Royal Theatre in Copenhagen in 1844. On autopsy, his death was attributed to the rupture of an atherosclerotic plaque in the left coronary artery. It was stated that the vessel wall contained 'several atheromatous plaques, one of which quite clearly had ulcerated, pouring the atheromatous mass into the arterial lumen'.

By the end of the 18th century, two theories dominated the discussion on the pathophysiology of atherosclerosis: the thrombogenic theory by Carl von Rokitansky and the inflammatory theory proposed by Rudolf Virchow.[5] Rokitansky proposed that the deposits observed in the inner layer of the arterial wall

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were derived primarily from fibrin and other blood elements rather than being the result of a purulent process. Subsequently, the atheroma resulted from the degeneration of the fibrin and other blood proteins and finally these deposits were modified toward a pulpy mass containing cholesterol crystals and fatty globules. Virchow's description of the pathogenesis of atherosclerosis was based on an in-depth study of the histological characteristics of the atherosclerotic lesion in all its stages. For the first time he utilised the term 'endarteritis deformans'. By this he meant that the atheroma was a product of an inflammatory process within the intima and that the fibrous thickening evolved as a consequence of a reactive fibrosis induced by proliferating connective tissue cells within the intima. He maintained that mechanical forces initiated the irritative stimulus and that the endarteritis was part of a repair mechanism. To date, Virchow's concept of local intima injury as the initiating irritative stimulus is still accepted and it has been extended to include other factors besides mechanical factors. Virchow's hypothesis formed the basis of the popular response-to-injury hypothesis of Russel Ross (1929-1999) which postulated that the lesions of atherosclerosis arise as a result of focal injury to arterial endothelium, followed by adherence, aggregation and release of platelets.[6]

Today we know that atherosclerosis is the result of a long-term, low-grade inflammation that leads to an interaction between cells of the immune system, proliferation of smooth muscle cells, and formation of fibrous tissue. According to the American Heart Association Committee on Vascular Lesions, plaque progression can be subdivided into different phases and different lesion types.[7,8] The final result is a lesion characterised by an accumulation of extracellular lipid and necrosis that becomes covered by a thin fibrous cap – a so-called vulnerable plaque. Vulnerable plaques are particularly prone to plaque rupture and thrombosis leading to clinical disease. Post-mortem studies have shown that vulnerable plaques have common characteristics: a thin fibrous cap (cap thickness <65 μm), a large lipid core, and increased macrophage activity. Molecular changes such as reduced collagen synthesis, localised imbalance of proteolytic activity, and smooth muscle cell apoptosis are most dominant at the plaque shoulder. In this region the mechanical stress is maximal and disruption tends to occur. Also, a growing body of evidence suggests that vasa vasorum neovascularisation is likely correlated with intraplaque haemorrhage which may lead to an increased size of the necrotic core, lesion instability and eventually plaque rupture. Despite many theories, the precise mechanism responsible for plaque rupture is unknown.

Diagnostic imaging in atherosclerosis

Since Seldinger invented a technique for the percutaneous placement of an access needle with catheters over guide wires in 1953, and Mason Sones (1919-1985) accidentally entered a patient's right coronary artery and injected 30 cc of contrast dye in 1958, angiography has been considered the gold standard in the assessment of atherosclerosis. It also set the stage for future therapeutic intervention such as bypass surgery and percutanous transluminal angioplasty. However, angiography illustrates only the contrast agent-filled lumen, but does not provide information about the vessel wall itself. Therefore, novel diagnostic imaging techniques have been developed to directly visualise the arterial wall and to characterise plaque composition.

Invasive imaging techniques

In order to visualise various plaque components to determine potential vulnerability of individual plaques, several invasive imaging modalities were developed including intravascular ultrasound (IVUS), optical coherence tomography (OCT) and intravascular magnetic resonance imaging (IVMRI).[9] Next to these techniques, the fact that a cholesterol-rich lipid core causes colour changes on the plaque surface combined with the unique energy absorption of its components resulted in the development of angioscopy, spectroscopy and palpography. Temperature heterogeneity arising from plaque inflammation led to the development of thermography.[9] Of all intravascular imaging techniques IVUS is the most mature and widely used. A comparison of different invasive imaging techniques to characterise atherosclerotic plaque composition is given in table 1.

Non-invasive imaging techniques

Non-invasive imaging techniques in the diagnosis of atherosclerosis are Doppler ultrasound (DUS), multi-slice computed tomography (MSCT) and magnetic resonance imaging (MRI).[9] The carotid artery and peripheral arteries are the primary site for vessel imaging by DUS because they lie at a depth in tissue which can be reached with ultrasound. Coronary artery imaging is challenging because high temporal resolution is needed to eliminate cardiac motion and a high spatial resolution to adequately visualise small coronary arteries. Especially the field of non-invasive coronary imaging has seen considerable progress in the last years. A comparison of different non-invasive imaging techniques to characterise atherosclerotic plaque composition is given in table 2.

Treatment for patients with atherosclerosis

Clinical disease associated with atherosclerosis includes coronary heart disease manifested by angina pectoris and myocardial infarction; cerebrovascular disease manifested by transient ischaemic attack and stroke; peripheral arterial disease manifested by intermittent claudication, and aortic atherosclerosis or aneurysm. Although cardiovascular diseases are the leading cause of death in the Western world, several reports have shown that mortality from cardiovascular disease has declined substantially over the last decades.[10] Approx-

Table 1. Invasive imaging modalities for atherosclerosis.

Imaging modality	Since year	Axial resolution (μm)	Physical property	Tissue penetration	Plaque characterisation	Disadvantages
IVUS	1971	100-200	Ultrasound	Good	Fibrous and calcified	Low sensitivity lipid-rich lesions
OCT	1996	2-10	Infrared light	Poor (2.0 mm)	Lipid-rich, fibrous and calcified	Creation of blood-free field
IVMRI	1997	160-300	Electromagnetic radiation	Good	Lipid-rich, fibrous, calcified and thrombus	Only large vessels (>2 mm)
Angioscopy	1985	NA	Visible light	No	Yellow lesion corresponds with vulnerable plaque	- Creation of blood-free field - Only large vessels (>2 mm)
Spectroscopy	1989	NA	Laser light	Poor (0.3 mm)	Lipid-rich and calcified	Background noise
Palpography	1993	NA	Ultrasound and mechanical stress	Poor	Identifies macrophages at foci with increased strain	Differentiating normal artery from early/ advanced plaque
Thermography	1996	500-1000	Thermal radiation	Poor	Identifies heat released by inflammation	- Temperature heterogeneity in relation to plaque vulnerability - Vessel wall injury

IVUS=intravascular ultrasound, OCT=optical coherence tomography, IVMRI=intravascular magnetic resonance imaging, NA=not applicable.

imately half of the decline in mortality is related to reductions in major risk factors and approximately half related to evidence-based medical therapies.

Risk factor modification and medical therapy

Primary and secondary prevention of atherosclerotic disease require management of modifiable risk factors for atherosclerosis, especially dyslipidaemia, hypertension, smoking, obesity and diabetes.[11] Risk factor modification by therapeutic lifestyle changes as well as drug therapies have been shown to decrease cardiovascular morbidity and mortality, and also reduce recurrent events and the need for interventional procedures in patients with established disease. Therapeutic lifestyle changes include diet improvement, smoking cessation and physical activity. The major drug therapies of proven benefit in patients with cardiovascular disease include aspirin, statins, angiotensin-converting enzyme (ACE) inhibitors and β-blockers.

Thrombolysis

In addition to risk factor modification and medical therapy, the development of therapeutics for atherosclerotic disease has focused on revascularisation of ischaemic regions. Thrombolysis can be regarded as a pharmacological reperfusion therapy for patients with acute cardiovascular event due to thrombosis on a plaque. Despite its proven efficacy in selected patients, many patients are ineligible (because of increased risk of bleeding, advanced age, haemodynamic instability

Table 2. Non-invasive imaging modalities for atherosclerosis.

Imaging technique	Since year	Resolution (μm)	Physical property	Tissue penetration	Plaque characterisation	Disadvantage
DUS	1966	100-200	Ultrasound	Moderate	Fibrous and calcified	- Little correlation echogenicity and symptomatic disease - Artefacts
MSCT	1998	400-600	Ionising radiation (X-ray)	Good	Calcified	- Low sensitivity noncalcified plaques - Radiation exposure
MRI	1992	250-300	Electro-magnetic radiation	Good	Lipid-rich and fibrous	- Long acquisition times - Motion artefacts

DUS=Doppler ultrasound, MSCT=multiple slice computed tomography, MRI=magnetic resonance imaging.

or duration of symptoms) or have persistent occlusion or re-occlusion of the infarct-related artery. Furthermore, new treatments to open an artery have been developed and are often used as primary treatment.

Bypass surgery and percutaneous interventions

Surgical methods for revascularisation were first developed in the late 1960s. In surgery, vascular grafts are used to bypass atherosclerotic plaques and hence reperfuse the tissue distal to the stenosis. Since the 1990s there is a tendency towards a less invasive treatment with less procedural mortality and morbidity. Therefore, percutaneous interventions including balloon angioplasty, stenting and several atheroablative technologies now dominate the field following the first angioplasty by Charles Dotter in 1963. In balloon angioplasty, an intravascular dilatation catheter is advanced towards the stenosis and then inflated to press the plaque into the arterial wall. Compared with surgery, these interventions require a shorter hospitalisation and recovery time, with a similar long-term survival rate in selected patients. However, there are three major challenges within the field of percutaneous interventions.[12] The first is acute success in enlarging the lumen of the vessel or creating a new channel in total occlusion. The second is preventing thrombotic occlusion of the treated segment using local or systemic methods, and the third is prevention of restenosis resulting from exaggerated proliferative response of the vessel wall to injury. The use of (drug-eluting) stents has contributed greatly to percutaneous interventions by reducing the risks of both acute vessel closure and late restenosis. Although stenting has become the most widely used percutaneous technique, other devices continue to be used for specific lesions and patient subsets. The technical safety and efficacy of atheroablative and thrombectomy devices have been described,[13] but few data exist to demonstrate incremental benefit with regard to clinical outcome.[12]

Non-invasive treatment

In response to the risk of invasive procedures and the challenges of percutaneous interventions, there is a continuous search for an effective, easy to perform and safe non-invasive treatment option in patients with atherosclerosis. To the best of our knowledge, there are currently no non-invasive therapies that target the atherosclerotic plaque itself. However, several attempts have emerged towards a non-invasive therapy for treating patients with chronic refractory angina pectoris, myocardial infarction or stroke.

Enhanced external counterpulsation

For patients with angina pectoris refractory to medical therapy who are not candidates for revascularisation, enhanced external counterpulsation (EECP) has become increasingly used worldwide as a non-invasive treatment option since it was developed in China about two decades ago.[14] It provides augmentation of diastolic and coronary blood flow similar to the intra-aortic balloon pump resulting in a decrease in myocardial oxygen demand and an increase in cardiac output. It utilises the serial inflation of three sets of cuffs wrapped around the calves, thighs and buttocks.[14] Treatment is administered one/two hours daily at least five days a week for a total of 35 hours. In the MUST-EECP study 139 patients with angina pectoris were randomised to inactive versus active EECP. EECP reduced angina and extended time to exercise-induced ischaemia.[15] Objective measures of coronary ischaemia have demonstrated improved time to ST-segment depression, stress myocardial perfusion,[16] and PET scan myocardial perfusion at rest and after dipyramidole.[17] Benefits have been demonstrated to be durable in many patients for up to five years after treatment.[18]

Extracorporeal shock wave therapy

Another proposed treatment for patients with severe coronary artery disease with no options for PCI or surgery is extracorporeal cardiac shock wave therapy (ECST). Shock wave therapy has been widely used in lithotripsy or in the treatment of certain orthopaedic conditions. Some studies have demonstrated that low-energy extracorporeal shock wave therapy could up-regulate angiogenic factors in cultured endothelial cells *in vitro*[19] and enhances angiogenesis in the ischaemic myocardium and normalises myocardial function in a porcine model of chronic myocardial ischaemia.[20] It has also shown to improve left ventricle remodelling after acute myocardial infarction in pigs when therapy is started in an early phase.[21] In nine patients with end-stage coronary artery disease ECST improved symptoms of myocardial ischaemia and also improved myocardial perfusion as evaluated by dipyridamole stress thallium scintigraphy without any major adverse effects.[22]

Low-energy laser irradiation

Several experimental studies have shown that low-energy laser irradiation (LELI) can be used as another non-invasive treatment option in myocardial infarction or stroke. LELI has been found to modulate various biological processes, including an increase in mitochondrial respiration and ATP synthesis, accelerate wound healing, and promote the process of skeletal muscle regeneration after injury. It was shown in an experimental model of the infarcted heart that LELI had a profound cardioprotective effect, resulting in a 50 to 70% reduction in infarct size six weeks after coronary artery occlusion.[23] This effect was partially attributed to a significant increase in the number of intact mitochondria and ATP content, as well as to antioxidative enzyme activity in LELI induced hearts of rats and dogs as compared with non-irradiated hearts. LELI applied transcranially six hours post-embolic stroke in rabbits and 24 hours postischemic stroke in rats caused a significant improvement in the neurological score over sham-operated experimental animals,[24] a finding that has been confirmed by others.[25]

It is thought that LELI causes suppression of nitric oxide synthase activity and upregulation of TGF-β1, which are considered neurotoxic and neuroprotective, respectively.

Ultrasound enhanced thrombolysis

The ability of ultrasound to enhance thrombolysis was already described in the 1970s. Since then, *in vitro* and *in vivo* studies have shown that thrombolysis with intravenous tPA can be enhanced with transcutanous ultrasound.[26,27] It is thought that ultrasound delivers mechanical pressure waves to the clot, thus exposing more thrombus surface to the circulating drug. Small clinical trials have shown promising results concerning the potential application of ultrasound-enhanced thrombolysis in acute cerebral ischaemia.[28,29] Moreover, the combination of intravenous gaseous microspheres (microbubbles) with ultrasound has been shown to be a potential alternative to recanalise intravascular thrombi. Recently, the first clinical trial has started regarding ultrasound enhanced thrombolysis using microbubbles in patients with acute ST-elevation myocardial infarction.[30]

Conclusion

Although non-invasive therapies are interesting treatment options for patients with atherosclerosis, the field is still in its infancy and more studies are needed to define its role in future. We believe the rapid changes in medical imaging will ultimately lead to innovations in image-guided non-invasive therapy for patients with atherosclerosis. ■

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